Attorney's Docket No.: 062[illegible]150003 / D 1841-3P US

#18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.* Art Unit : 1617
Serial No. : 10/010,283 Examiner : Jennifer Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

MAIL STOP APEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

(1) Real Party in Interest

The Real Party in Interest is AstraZeneca AB, SE-151 85 Södertälje, SWEDEN.

(2) Related Appeals and Interferences

There are no pending related appeals or interferences.

(3) Status of Claims

Claims 1-8 and 10 are canceled.

Claims 9 and 11-25 are rejected and under appeal.

(4) Status of Amendments

All previously filed amendments have been entered. No amendments are being submitted herewith.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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(5) Summary of Invention

The invention relates to methods for treating patients suffering from chronic obstructive pulmonary disease (COPD). The methods include administering a combination of formoterol and budesonide, in a molar ratio of 1:2500 to 12:1, by inhalation. The therapeutic agents can be administered simultaneously, sequentially or separately.

(6) Issues

Are the claims obvious in light of WO 93/11773 (Carling *et al.*), in view of Cazzola *et al.*, and Nederland Tijdschrift Voor Geneeskunde, in view of Saunders Manual of Medical Practice?

(7) Grouping of Claims

The claims should stand or fall together.

(8) Argument

The claims are not obvious in light of WO 93/11773 (hereafter, Carling *et al.*), in view of Cazzola *et al.*, and Nederland Tijdschrift Voor Geneeskunde, in view of Saunders Manual of Medical Practice.

Applicants' claims are directed to methods of treating a patient suffering from COPD using a combination of formoterol and budesonide in a ratio of from 1:2500 to 12:1.

In the final Office action, mailed January 29, 2003, the Examiner maintained a rejection of the claims (claims 9 and 11-25) under 35 U.S.C. §103(a) as being unpatentable over Carling *et al.* (of record), Cazzola *et al.* (reference U), and Nederlands Tijdschrift voor Geneeskunde (reference V), in view of Saunders Manual of Medical Practice (reference W).

In the first Office action, mailed January 29, 2002, the Examiner summarized her understanding of these references as follows: Carling *et al.*, "teach a medicament containing effective amounts of formoterol and budesonide in combination for simultaneous, sequential or separate administration by inhalation in treatment of respiratory disorder"; reference (U), in the abstract, teaches the use of formoterol to treat patients with COPD; reference (V) teaches the

inhalation of budesonide to treat chronic obstructive pulmonary disease; and reference (W) teaches in the contents that COPD is a respiratory disorder (Office action of January 29, 2002, pp. 4-5).

The Examiner further stated at page 5 of the January 29, Office action,

> it would have been obvious to the skilled artisan to employ the Carling's medicament in treatment of COPD since COPD is well known respiratory disease as disclosed by the W reference. Further, each of active agents (budesonide and formoterol) utilized in Carling's medicament are individually known to treat COPD. Therefore it would be expected that the medicament of Carlings would treat COPD conditions as well. The skilled artisan would have been motivated to employ Carling's medicament in treatment of COPD with reasonable expectation of success since each of the active agents utilized in Carling's medicament are well known individually for treating respiratory disease, COPD.

Applicants respectfully disagree. One of the requirements for establishing a *prima facie* case of obviousness is to establish that there would have been "a reasonable expectation for success" (MPEP 2142) based on the prior art 'at the time the invention was made' (MPEP 2141.01 (III)).

> It is difficult but necessary that the decisionmaker forget what he or she has been taught...about the claimed invention and cast the mind back to the time the invention was made..., to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art. *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. Denied, 469 U.S. 851 (1984).

This requirement has not been met. In light of the prior art at the time the invention was made, including the references cited by the Examiner, there would not have been a reasonable expectation of success regarding the treatment of COPD with a combination of budesonide and formoterol. Carling *et al.* does not teach or suggest that his combination of formoterol and budesonide is suitable for treating COPD. Carling *et al.* mentions that his combination of formoterol and budesonide is suitable for treating "respiratory diseases," and the only specific respiratory disease mentioned is asthma. Asthma and COPD are two separate and distinct

diseases. Airway inflammation in COPD, for example, differs from airway inflammation in asthma (Jeffrey PK, *Thorax* 53:129-36, 1998). The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma, but their usefulness in COPD is much less certain. Therefore, by teaching the use of a combination of budesonide and formoterol to treat a respiratory disease such as asthma, Carling *et al.* does not teach or suggest using the same combination for the treatment of COPD.

According to reference V, "[i]nhalation corticosteroids are of great importance in the treatment of asthmatic patients. Their place in the treatment of patients with COPD is much less clear." In this study, patients suffering from COPD were treated with budesonide, and subsequently, half (n=2) of the patients developed a pulmonary infection caused by *Mycobacterium malnoense,* and the other half (n=2) of the patients developed a pulmonary infection caused by Aspergillus. Reportedly, the patients did not have an immunological deficiency or anatomical pulmonary or bronchial deformation, which could have explained the occurrence of these infections. The authors of reference V suggested that "[t]he high doses of inhalation corticosteroids may have been involved in the cause of these infections by suppressing the T-cell response locally" (see abstract). The authors concluded that, "[i]n view of this, longterm inhalation corticosteroid treatment should be prescribed in COPD patients only if the efficacy of the medication has been proved in the individual patient."

While reference U teaches that treatment with formoterol alone can increase FEV in COPD patients by up to 15%, in light of the teachings of reference V, it certainly would not have been obvious to combine budesonide with formoterol, or *any* other drug, for the treatment of COPD. In fact, one of ordinary skill in the art might have concluded that the prescription of budesonide to treat COPD would be a treatment-of-last-resort, given the increased risk of opportunistic pulmonary infections. Thus, in light of the art cited by the Examiner, there would have been no reason for the artisan to expect treatment of COPD with a combination of budesonide and formoterol to be successful.

The unexpected nature of Applicants' discovery that COPD can be successfully treated with a combination of budesonide and formoterol is further evidenced by the Declaration of Jan Trofast ("the Trofast declaration"), submitted with Applicants' reply filed April 25, 2002. The Trofast declaration also supports Applicants' position that Carling's teaching of the use of

budesonide and formoterol to treat asthma would not have suggested their use to treat COPD. In this declaration, Dr. Trofast explained the difficulties of treating COPD and the general lack of enthusiasm for the treatment methods (including the use of glucocorticoids, such as budesonide, and steroids) in existence at the time the application was filed. In particular, Dr. Trofast discussed two published studies illustrating the low efficacy of glucocorticoids, such as budesonide, in treating COPD, particularly in comparison to their efficacy in treating asthma. The Pauwels *et al.* study reported the overall effect of three years of treatment with budesonide on the forced expiratory volume (FEV) of patients with mild COPD to be "...quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma..." (emphasis added; Pauwels *et al.*, "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," *The New England Journal of Medicine*, 340:25, pp. 1948-1953, June 24, 1999; submitted as Exhibit B with the Reply). The Niewoehner study demonstrated that the benefits of systemic glucocorticoids in treating acute exacerbations of COPD were much smaller than the benefits of glucocorticoids in the treatment of severe exacerbations of asthma (Niewoehner, "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease," *The New England Journal of Medicine*, 340:25, pp. 1941-1947, June 24, 1999; submitted as Exhibit C with the reply).

Furthermore, in his declaration, Dr. Trofast presented data indicating that treatment of COPD with both budesonide and formoterol was more effective than treatment with either drug alone. These results were manifested by the improved effects of two COPD phenotypes: (i) a reduction in severe exacerbations, and (ii) an improvement in forced expiratory volume (FEV).

The Examiner responded to the Applicants' April 25, 2002, reply with an Office action mailed on July 30, 2002, in which the rejection of the claims (claims 9 and 11-25) under §103(a) was maintained. The Examiner complained of a lack of "independent data by which the Examiner can make a reasonable determination of synergistic effect is present on the combination of budesonide/formoterol gives greater than additive effect in treatment of COPD" (Office action, pp. 2-3), stating that:

> ...data [in the Trofast declaration] is sufficient to show that combination of budesonide/formoterol-treated patients had a significant improvement compared to the patients treated with either budesonide alone or formoterol alone. However, there is no

> independent data by which the Examiner can make a reasonable determination of synergistic effect...

In a reply filed on December 2, 2002, Applicants answered the Examiner's rejection by reiterating the nonobviousness of treating COPD with a formoterol/budesonide combination in view of Carling *et al.*, combined with the teachings of references U, V, and W. Furthermore, and in direct response to the Examiner's request for evidence of synergism, Applicants submitted a declaration of Christer Hultquist, M.D. The declaration provided data demonstrating a synergistic effect of the combination treatment on the severe exacerbations phenotype as well as on the morning peak expiratory volume (FEV) phenotype.

Finally, in the final Office action, mailed January 29, 2003, the Examiner again maintained the obviousness rejection, this time asserting that the evidence of synergism provided in the declaration "is not commensurate in scope with the breadth of the claims sought to be patented" (Final Office action, p. 2). In support of this assertion, the Examiner cited three cases, *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978); *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); and *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972).

The application at issue in *In re Kulling* related to the treatment of a solution in a process for the production of titanium dioxide. In this case, a declaration filed by the Applicants to overcome a reference cited in an obviousness rejection was deemed insufficient, because the process and results disclosed in the declaration did not read on the claims, and therefore the evidence was not commensurate in scope with the breadth of the claims sought to be patented. Because *In re Kulling* addresses a different issue, *i.e.*, the relevance of the evidence to the claimed subject matter, Applicants submit that this case is not relevant, and will address the following rebuttal to the Greenfield and Lindner cases.

Applicants respectfully submit that the Examiner has misapplied the case law, a direct result of her misplaced emphasis on the importance of synergism to the patentability of Applicants' claims. In each of *In re Greenfield* and *In re Lindner*, the patent applications at issue claimed a combination of compounds. In each case, the Examiner rejected the claims because each individual compound had been described in the prior art, performing the same or a similar

function as the same compound did in the combination claimed in each of the Greenfield or Lindner applications. In each of these cases, the Applicant submitted a declaration that demonstrated synergism, and the Examiner responded by declaring that the evidence presented by the declaration was not "commensurate in scope with the breadth of claims."

In contrast, in the present case, the prior art did not teach that COPD could be treated successfully with budesonide individually. As discussed above, reference V discloses adverse effects on a patient with COPD who is treated with budesonide alone. Thus it would not have been expected from reference V that budesonide could be combined with any other compound, or formoterol in particular, to effectively treat COPD.

Applicants maintain that there is nothing in the cited references, Carling *et al.*, U and V in particular, to suggest that a COPD patient would get any beneficial effect by taking a combination of budesonide and formoterol, much less "an additive" effect equivalent to that disclosed by the Trofast declaration. While reference V discloses that COPD patients receive budesonide treatment, the reference does not report *any* positive effect on *any* COPD phenotype. Therefore, a combination of the teachings in references V and U would not lead one to conclude that a combination of budesonide and formoterol would lead to a reduction in severe exacerbations and an improvement in FEV, as demonstrated by the Trofast declaration. Thus, the Examiner's further request for evidence of a synergistic effect was unfounded.

Applicants maintain that the declaration of Jan Trofast, submitted April 25, 2002, is sufficient evidence of unexpected results to overcome the Examiner's rejection in view of the cited art. The declaration of Dr. Hultquist on December 13, 2002, is further evidence to overcome the rejection. Applicants also maintain that the Examiner's requirement for evidence of a synergistic effect in light of the data presented in the first declaration was unfounded, and the subsequent objection to the declaration of Dr. Hultquist because the results must be commensurate in scope with the claims was misplaced.

As discussed *supra*, the Examiner's rejection must be based on the knowledge of one having ordinary skill in the art at the time the application was filed. The Examiner requested proof of a synergistic effect based on Applicant's own teachings, including the teachings of the Trofast declaration, and not on the teachings of the prior art. The declaration of Dr. Trofast provides evidence of a surprising result: the successful treatment of COPD using a combination

of budesonide and formoterol. At the time the application was filed, it was not understood that the two compounds would have any therapeutic effect on COPD when administered individually or in combination. Accordingly, the Examiner has not established *prima facie* obviousness, and Applicant is not required to demonstrate synergism.

Applicants maintain, as originally set forth, that the references cited by the Examiner do not render the treatment of COPD with this combination as obvious, and request that the rejection under 37 U.S.C. §103 be withdrawn.

The brief fee of $320 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003.

Respectfully submitted,

Date: Sept. 26, 2003

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Appendix of Claims

9. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease, which method comprises administering to the patient via inhalation, simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a dose of a second active ingredient which is budesonide, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.

11. A method according to claim 9, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.

12. A method according to claim 9, wherein the first active ingredient is formoterol fumarate dihydrate.

13. A method according to claim 9, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:555 to 2:1.

14. A method according to claim 13 wherein the molar ratio is from 1:70 to 1:4.

15. A method according to claim 9 further comprising providing the doses to the patient in the form of a dry powder.

16. A method according to claim 15 wherein the first and second active ingredients are formulated as powder particles having a mass median diameter of less than 10 μm.

17. A method according to claim 9 wherein the first and second active ingredients are provided in the form of an admixture.

18. A method according to claim 9 wherein the doses are administered separately, less than about 2 hours apart.

19. A method according to claim 18 wherein the doses are administered separately, less than about 30 minutes apart.

20. A method according to claim 19 wherein one dose is administered immediately after the other.

21. A method according to claim 9 wherein the amount of the dose of the first active ingredient is from about 2 to 120 nmol.

22. A method according to claim 21 wherein the amount of the dose of the first active ingredient is from about 7 to 70 nmol.

23. A method according to claim 9 wherein the amount of the dose of the second active ingredient is from about 0.1 to 5 μmol.

24. A method according to claim 23 wherein the amount of the dose of the second active ingredient is from about 0.15 to 4 μmol.

25. A method according to claim 12 wherein the amount of the dose of formoterol fumarate dihydrate is from about 1 to 50 μg.